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Some Organic Compounds of Mercury

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
OF NORTHWESTERN UNIVERSITY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

BY
EDMUND BURRUS MIDDLETON

EASTON, PA.:
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SOME ORGANIC COMPOUNDS OF MERCURY[1,2]

Very few mercury derivatives of aromatic esters are known. These have been prepared by direct mercurization of the esters by mercuric acetate. Methyl benzoate gives mono- and dimercurated compounds, the structures of which have not been definitely established.[3] *o*-Chloromercuribenzoic methyl ester has been obtained from methyl alcohol and sulfidemercuri-benzoyl chloride.[4] The esters of *ortho-* and *para*-aminobenzoic acids and their mono- and di-alkyl derivatives give mono- and dimercurated compounds.[5] Esters of salicylic acid react with mercuric acetate giving mono-mercurated compounds.[6]

Mercurated acid chlorides were unknown until recently, when *o*-chloromercuri-benzoyl chloride was prepared from thionyl chloride and the

[1] Presented at the Rochester Meeting of the American Chemical Society, April 1921.

[2] This work was done under a grant from the United States Interdepartmental Social Hygiene Board, Washington, D. C., Dr. Valeria H. Parker, Secretary. Some of the organic mercury compounds prepared will be tested for their pharmaceutical value by Dr. A. S. Loevenhart of the University of Wisconsin.

[3] Schoeller and Schrauth, *Ber.*, **53,** 636 (1920).

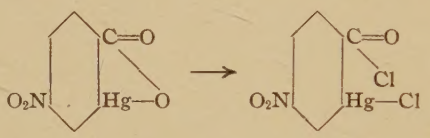
[4] Sachs, *ibdi.*, **53,** 1741 (1920).

[5] Schoeller and Hueter, *ibid.*, **47,** 1930 (1914). Schoeller, Schrauth and Liese, *ibid.*, **52** 1777 (1919). Ref. 3, p. 634.

[6] Ref. 3, p. 639.

anhydride of *o*-hydroxymercuri-benzoic acid.[4] Undoubtedly, it was thought that halides of phosphorus could not be used for making acid chlorides containing mercury, as it has long been known that these halides react with organomercury compounds with the elimination of the mercury.[7] During the first part of the present work thionyl chloride was used, but it was soon found possible to use phosphorus pentachloride without removing the mercury from the molecule.

The present paper is a report of the preparation and properties of a number of esters and other derivatives of mercurated *p*-nitrobenzoic acid obtained from the corresponding mercurated acid chloride. When the mercuric salt of *p*-nitrobenzoic acid is heated to 200° it gives the inner anhydride of *o*-hydroxymercuri-*p*-nitro-benzoic acid.[8] The anhydride suspended in chloroform reacts with phosphorus pentachloride to give the desired acid chloride.



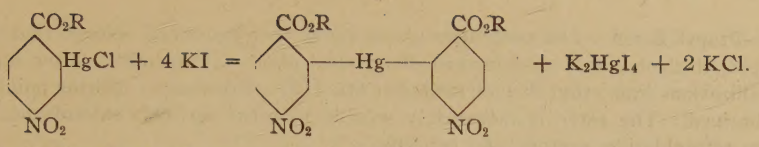
It was found difficult to obtain the acid chloride in a form pure enough for analysis. The derivatives were prepared directly from the crude product. The *n*-butyl, *n*-propyl, *iso*propyl, ethyl and methyl esters were made from the alcohols and the crude chloride. The melting points of these compounds increase regularly from the *n*-butyl ester to the methyl ester. The acid chloride was also treated with ethylene chlorohydrine, ethylene bromohydrine, and diethylamino-ethyl alcohol. Esters were formed in each case, but only the first of these has as yet been obtained in pure form. The chloride reacted normally with aniline giving an anilide.

The action of inorganic iodides on the mercurated esters was studied. The reaction consists in the change of the compounds of the type, RHgX, to those of the type, R_2Hg. The mercurated esters thus resemble the mercurated hydrocarbons, the mercurated dimethylanilines, and the acetylated mercury phenols, rather than the free mercury phenols from which the mercury is entirely removed by the action of inorganic halides.[9] An equivalent amount of alkali is formed during this removal of mercury. In the case of the mercurated esters no alkali is formed. The reaction is as follows

[7] Buckton, *Ann.*, **108,** 105 (1858). Cahours, *Ber.*, **6,** 568 (1875). Michaelis, *Ann.*, **293,** 196, 248, 303 (1896).

[8] Blumenthal, *Biochem. Z.*, **32,** 60 (1911).

[9] Whitmore, J. *Am. Chem. Soc.* **41,** 1841 (1919). Whitmore and Middleton, *ibid.*, **43,** 622 (1921).

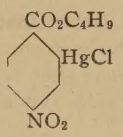


These derivatives of mercury diphenyl are less soluble than the corresponding chlorides and their melting points are higher. They react in the usual way with mercuric chloride forming the compounds of the type, RHgCl. They can be saponified without breaking the C-Hg linkage. The acid obtained by this process is *o*-mercuri-*bis*(*p*-nitrobenzoic acid), which has been prepared by a regulated alkaline reduction of *o*-hydroxymercuri-*p*-nitrobenzoic acid.[8]

The acid chloride prepared by Sachs was also prepared by means of phosphorus pentachloride. The *n*-butyl ester prepared from it was identical with that prepared from a sample of the acid chloride made with thionyl chloride.

Experimental

The mercuric salt of *p*-nitrobenzoic acid was prepared from the sodium salt by precipitation with a nearly neutral solution of the calculated amount of mercuric nitrate. The precipitate was washed thoroughly and dried. Fifty g. of the mercuric salt was heated for 3 hours at 200–220° in a small flask immersed in an oil-bath. When samples of more than 100 g. were heated, explosions sometimes occurred. After heating the mixture, it was cooled and the *p*-nitrobenzoic acid which formed was removed by repeated extractions with small amounts of ether. The residue insoluble in ether consisted of the nearly pure anhydride of *o*-hydroxymercuri-*p*-nitrobenzoic acid.

***n*-Butyl Ester of *o*-Chloromercuri-*p*-nitrobenzoic acid,** 

.—Ten g. of the anhydride was suspended in 100 cc. of chloroform and treated in the cold with 7 g. of phosphorus pentachloride. Vigorous action ensued. The mixture was then heated under a reflux condenser about 30 minutes. The solution was then cooled and filtered. The precipitate was washed with chloroform to remove phosphorus oxychloride and allowed to dry. The dry acid chloride was then treated with 10 cc. of *n*-butyl alcohol and heated until it completely dissolved. As this product cooled, white crystals of the *n*-butyl ester separated. These are fairly soluble in ethyl alcohol, benzene, chloroform, acetone, ether, and carbon tetrachloride. The product was recrystallized from hot ethyl alcohol until it showed a constant melting point of 125–126° (uncorr.). Nine g. of the ester was obtained from 10 g. of the crude anhydride; yield, 70%. Most of the loss occurs in the conversion of the acid to the acid chloride which is never complete.

Analyses. Subs., 0.1754: Hg, 0.0770. Subs., 0.1991, 0.2033: CO_2, 0.2071, 0.2146. Calc. for $C_{11}H_{12}O_4NClHg$: C, 28.8; Hg, 43.8. Found: C, 28.4, 28.8; Hg, 43.9.[10]

[10] The analyses for mercury were carried out by the "gold crucible method" de-

n-**Propyl Ester.**—The procedure given above was employed, except that 10 cc. of *n*-propyl alcohol was used instead of butyl alcohol. The product, after repeated crystallizations from ethyl alcohol, melted at 145–150°. No sharper melting point could be obtained. The ester is moderately soluble in ethyl alcohol, chloroform, ether, carbon tetrachloride, acetone and benzene.

Analyses. Subs., 0.1943, 0.1911: Hg, 0.0887, 0.0871. Calc. for $C_{10}H_{10}O_4NClHg$: Hg, 45.2. Found: 45.6, 45.6.

*Iso*propyl Ester.—The same procedure was used as with the other esters. The purified product melted at 179–180°.

Analyses. Subs., 0.1981, 0.2089: Hg, 0.0897, 0.0943. Calc. for $C_{10}H_{10}O_4NClHg$: Hg, 45.2. Found: 45.3, 45.1.

Ethyl Ester.—The purified product melted at 220–222°. Its properties and solubilities are similar to those of the other esters.

Analyses. Subs., 0.1945, 0.1800: Hg, 0.0899, 0.0842. Calc. for $C_9H_8O_4NClHg$: Hg, 46.6. Found: 46.2, 46.8.

Methyl Ester.—The product, purified by crystallization from methyl alcohol, melted at 240–245°.

Analyses. Subs., 0.2206, 0.2008: Hg, 0.1077, 0.0976. Calc. for $C_8H_6O_4NClHg$: Hg, 48.2. Found: 48.9, 48.6.

Chloro-ethyl Ester.—This ester was prepared from the crude acid chloride and ethylene chlorohydrine in the usual way. Its solubilities and properties resembled those of the other esters. Crystallization from ethyl alcohol gave a product melting at 163–164°.

Analyses. Subs., 0.2010, 0.2023, 0.2323: Hg, 0.0865, 0.0879, 0.1000. Calc. for $C_9H_7O_5NCl_2Hg$: Hg, 43.2. Found: 43.0, 43.4, 43.1.

Attempts at Preparation of the Bromo-ethyl and Alkamine Esters

The acid chloride was found to react readily with ethylene bromohydrine and with diethylamino-ethyl alcohol, but no homogeneous product was obtained from either reaction. Further attempts are being made to prepare these esters in a state of purity.

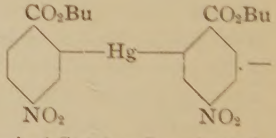
Determination of the Position of the Mercury in the Esters

When the mercurated esters reacted in the cold with bromine water, they gave products which, after saponification and acidification, were converted into *o*-bromo-*p*-nitrobenzoic acid; this was identified by its melting point (163°) and by analyses for bromine.

Anilide of *o*-Chloromercuri-*p*-nitrobenzoic Acid.—Ten g. of the crude acid chloride was heated with 6 cc. of aniline until solution took place. The anilide separated as the mixture cooled. It was washed free from aniline with benzene and recrystallized from ethyl alcohol. The product was soluble in hot ethyl alcohol, slightly soluble in ether and insoluble in most other organic solvents.

Analyses. Subs., 0.2112, 0.2001: Hg, 0.0878, 0.0832. Calc. for $C_{13}H_9O_3N_2ClHg$: Hg, 42.0. Found: 41.6, 41.6.

n-**Butyl Ester of *o*-Mercuri-*bis*(*p*-nitrobenzoic Acid),**



scribed on p. 365 of "Organic Compounds of Mercury" (Chemical Catalog Co., N. Y. C. 1921) by one of us (W.). In the analysis of organic mercury compounds containing nitro groups the heating must be carried out very cautiously to avoid slight explosions which are likely to blow foreign material against the amalgam.

Eight g. of the *n*-butyl ester of *o*-chloromercuri-*p*-nitro-benzoic acid in 100 cc. of ethyl alcohol was refluxed with 5 g. of potassium iodide for 1 hour. As the reaction mixture cooled, the mercuri-*bis* compound separated in colorless crystals. The mother liquor contained large amounts of inorganic mercury. The product was recrystallized from ethyl alcohol; m. p., 158°; yield, 5 g. or 95%. Its solubilities resembled those of the corresponding chloromercuri compound but were slightly less.

Analyses. Subs., 0.2521, 0.1461: Hg, 0.0791, 0.0459. Subs., 0.1781, 0.2214: CO_2, 0.2585, 0.3240. Calc. for $C_{22}H_{24}O_8N_2Hg$: C, 40.9; Hg, 31.1. Found: C, 39.6, 39.9; Hg, 31.4, 31.4.

One g. of this compound was heated with 0.43 g. of mercuric chloride (one mol) in 50 cc. of ethyl alcohol for 30 minutes. The corresponding chloromercuri compound, 1.2 g. separated as the product cooled; m. p., 125°. The chloride was analyzed.

Analysis. Subs., 0.1923: Hg, 0.0839. Calc. for $C_{11}H_{12}O_4NClHg$: Hg, 43.8. Found: 43.7.

Five g. of the ester of the mercuri-*bis* compound suspended in 100 cc. of ethyl alcohol was heated with 5 g. of sodium hydroxide. When all of the solid had dissolved, the solution was cooled. The sodium salt which separated was collected, dissolved in water, and the solution acidified. The amorphous precipitate was *o*-mercuri-*bis*(*p*-nitrobenzoic acid),[8] as was shown by analyses for mercury.

***n*-Propyl Ester.**—Seven g. of the corresponding chloromercuri ester was heated under a reflux condenser with 5 g. of potassium iodide in 100 cc. of alcohol for 1 hour. Colorless crystals of the mercuri-*bis* compound separated as the solution cooled. After recrystallization from ethyl alcohol, it melted at 189°; yield 4.6 g., or 92%.

Analyses. Subs., 0.1638, 0.1705: Hg, 0.0538, 0.0549. Calc. for $C_{20}H_{20}O_8N_2Hg$: Hg, 32.5. Found: 32.8, 32.2.

Treatment of this compound with mercuric chloride in alcohol gave the *n*-propyl ester of *o*-chloromercuri-*p*-nitrobenzoic acid melting at 145–150°.

Ethyl Ester.—This ester was prepared in the same way as were the *n*-butyl and *n*-propyl esters and resembled them in properties; m. p., 227–232°.

Analyses. Subs., 0.1909, 0.1877: Hg, 0.0650, 0.0644. Calc. for $C_{18}H_{16}O_8N_2Hg$: Hg, 34.1. Found: 34.1, 34.3.

***n*-Butyl Ester of *o*-Chloromercuri-benzoic Acid.**—Seven g. of the anhydride of *o*-hydroxymercuri-benzoic acid was treated with 5 g. of phosphorus pentachloride in 50 cc. of chloroform. Vigorous action took place. As soon as this had ceased, the mixture was cooled and the acid chloride was collected on a filter. It was washed with chloroform and allowed to dry. The product was heated with 10 g. of *n*-butyl alcohol until all of it dissolved. After several recrystallizations from alcohol it melted at 115°.

Two g. of the *o*-chloromercuri-benzoyl chloride prepared by the thionyl chloride method[4] was treated with *n*-butyl alcohol in the same way. The purified product melted at 116°. The melting point of the mixture of the two products was not lower.

Analysis. Subs., 0.1668: Hg, 0.0813. Calc. for $C_{11}H_{13}O_2ClHg$: Hg, 48.4. Found: 48.7.

Summary

1. Phosphorus pentachloride can be used as well as thionyl chloride for making acid chlorides of mercurated aromatic acids.

2. The acid chloride of *o*-chloromercuri-*p*-nitrobenzoic acid was used to prepare the following esters of the acid: methyl, ethyl, *n*-propyl, *iso*-propyl and *n*-butyl.

3. These compounds react with inorganic iodides to form the corresponding compounds of the type, R_2Hg.

4. These compounds can be saponified without breaking the C-Hg linkage.

This work was carried out under the direction of Professor Frank C. Whitmore. The author desires to thank him for his advice and criticism.

[Reprinted from the Journal of the American Chemical Society,
Vol. XLIII. No. 3. March, 1921.]

[Contribution from the Chemical Laboratory of Northwestern University.]

REACTION OF ALKALI HALIDES WITH MERCURY DERIVATIVES OF PHENOL.[1]

By F. C. Whitmore and Edmund Burrus Middleton.

Received November 22, 1920.

Mercury derivatives of phenol lose their mercury quantitatively when treated with a solution of potassium iodide. Ordinarily, an aromatic mercury compound does not react with iodides to give mercuric iodide. Under some conditions, one half of the mercury is removed as the iodide and the other half remains combined in a derivative of mercury diphenyl, $2R-Hg-I + 2KI = K_2HgI_4 + R_2Hg$. In a study of the mercury derivatives of *p*-bromo-dimethylaniline,[2] it was found that the reaction of potassium iodide with 5-bromo-2-dimethylamino-phenylmercuric acetate gave a considerable amount of *p*-bromo-dimethylaniline as well as the expected mercury diphenyl derivative. The formation of metallic mercury during the reaction made it appear that the alcohol or some other substance was acting as a reducing agent. However, this could not explain the formation of all of the bromo-dimethylaniline, since the amount of this substance produced was greater than the free mercury would require. A search through the literature revealed a number of cases in which mercury attached to carbon is replaced by hydrogen under the influence of iodide solutions. While this reaction is universal for Hg–N compounds, it is unusual for Hg–C compounds. Since there is undoubtedly some relation between the therapeutic value of mercury carbon compounds and the stability of the Hg–C linkage, it seemed desirable to study the conditions under which this linkage between mercury and carbon is broken by inorganic halides.

Biilmann found that mercury derivatives of malonic acid and of its esters[3] when treated with potassium iodide solution yield mercuric iodide and one molecule of potassium hydroxide for every Hg–C linkage. With potassium iodide mercury is removed in a different way from the products of the action of mercuric salts upon various unsaturated acids.[4] In this case the original unsaturated acid is recovered. The difference in the 2 reactions may be shown by the equations

$$R-Hg-I + 3KI + H_2O = RH + K_2HgI_4 + KOH$$

$$R-CHOH-CHHgI-CO_2K + 3KI = R-CH=CH-CO_2K + K_2HgI_4 + KOH.$$

[1] Part of this work was done under a grant from the U. S. Interdepartmental Social Hygiene Board, Dr. T. A. Storey, Secretary. Presented before the Organic Division of the American Chemical Society at the Chicago Meeting, September 1920.

[2] This Journal, **41**, 1851 (1919).

[3] Biilmann, *Ber.*, **35**, 2581 (1902); **42**, 1070 (1909).

[4] Biilmann, *ibid.*, **35**, 2571 (1902); **43**, 568 (1910); also compare Manchot, *Ann.*, **420**, 183 (1920).

In the second case the replacement of the mercury by hydrogen is accompanied by, or followed by, the loss of water. The mercury derivative of cyano-acetic acid[1] behaves in a manner similar to that of the mercury malonic derivatives. The mercury derivative of camphor[2] is said to be "decomposed" rapidly by an acetone solution of potassium iodide.

In the aromatic series a few cases of this replacement are recorded. Dimroth found that *p*-aminophenylmercuric acetate,[3] when treated with potassium iodide gave a small amount of inorganic mercury. This may be due to the formation of mercuric iodide during the formation of the mercury diphenyl derivative, or during a splitting of the Hg-C linkage, accompanied by the formation of aniline and alkali. Pesci found that salts of *o*-(chloromercuri)benzoic acid[4] when treated with sodium halides give sodium benzoate, mercuric halide, and sodium hydroxide.

2-5-Cresylmercuric acetate[5] is said to be "decomposed" by potassium iodide. Brieger and Schulemann in their exhaustive study of the mercuration of the various naphthalene intermediates[6] of the coal tar dye industry found that the mercurated naphthols are very sensitive to alkali halides. In some cases they titrated the alkali formed and drew conclusions as to the completeness of the splitting of the Hg-C linkage. They found that potassium iodide gives a quantitative replacement, while the bromide and chloride give it to a decreasing extent. In other cases they did not determine the alkali formed, but studied the "loosening" effect of the halide by treating with sulfides. In many instances, the pure mercury compound gave no action with ammonium sulfide, but, when treated with potassium iodide and then with the sulfide, gave mercuric sulfide. The bromide and chloride of potassium had a similar but weaker effect. Brieger and Schulemann found that the mercurated naphthylamines were split much less readily than the corresponding naphthols.

In view of the many cases of this peculiar replacement of organic mercury, and the lack of details, it seemed desirable to study the reaction with some substances simpler than the complicated intermediates used by Brieger and Schulemann. The mercurated phenols[7] prepared by Dimroth offered an ideal subject for the study.

Dimroth's method of treating a solution of phenol with mercuric acetate solution was discarded because of the large amount of dimercurated product formed. It was found that phenol, without a solvent, heated

[1] Petterson, *J. prakt. Chem.* [2] **86**, 458 (1912).

[2] Marsh and Fleming-Struthers, *J. Chem. Soc.*, **95**, 1777 (1909).

[3] *Z. anorg. Chem.*, **33**, 314 (1903).

[4] Pesci, *Gazz. chim. ital.*, **32**, II, 277 (1902); *Centralbl*, **1902**, II, 1454.

[5] Dimroth, *Ber.*, **35**, 2853 (1902). Compare Brieger and Schulemann, *J. prakt. Chem.*, [2] **89**, 104 (1914).

[6] *Ibid.*, 97 ff.

[7] *Habilitationsschr.*, Tubingen, 1900; *Centralbl.*, **1901**, I, 452; *Ber.*, **35**, 2855 (1902).

with mercuric acetate on the steam-bath gives a mixture of the *ortho* and *para* compounds free from the disubstituted product. These were separated by Dimroth's method of forming the chlorides; the *p*-hydroxyphenylmercuric chloride is insoluble in hot water, while the *ortho* compound is soluble. At temperatures above that of the steam-bath, the total yield was decreased somewhat, but the amount of *ortho* compound increased slightly.

The 3 mercurated phenols were boiled with aqueous potassium iodide. In each case the solid soon dissolved and the solution became alkaline. After boiling for 30 minutes the alkali was titrated with standard acid and phenolphthalein. The *ortho* and *para* compounds gave almost one molecule of alkali while the *di-* compound gave almost 2.

$$HO\text{–}C_6H_4\text{–}HgCl + KI + H_2O = HO\text{–}C_6H_5 + K_2HgI_4 + KOH + KCl.$$

The dimercuric chloride compound would give 2 molecules of potassium hydroxide. When potassium bromide was used in place of the iodide, only a small amount of alkali was formed. Potassium chloride gave no alkali even on prolonged boiling.

It seemed desirable to find out whether this unusual removal of mercury from the aromatic nucleus depended on the presence of the phenolic hydroxyl. To answer this question the acetyl derivatives of the *o-* and *p*-hydroxyphenylmercuric chlorides were prepared and treated with potassium iodide. There was no splitting of the Hg-C linkage in these cases. The solutions remained neutral. If splitting had occurred the alkali formed would probably have saponified the phenyl acetate to form sodium acetate and free phenol. No phenol was obtained as was shown by distillation of the neutral mixture with steam and a test of the distillate with ferric chloride. The acetylated *o*-hydroxyphenylmercuric chloride reacted with aqueous potassium iodide to form the organomercuric iodide. The hot mother liquor from this iodide gave a small amount of the corresponding mercury diphenyl derivative, *o,o'*-mercuri-bis(phenyl acetate). The same reaction, carried out in alcohol solution, gave only the iodide. The acetylated *p*-hydroxyphenylmercuric chloride gave only the corresponding iodide.

As the yield of the substituted mercury diphenyl is often larger with sodium thiosulfate than with potassium iodide, the former reaction was tried with the acetylated mercury phenols. In each case, a fair yield of the mercury diphenyl derivative was obtained. The proof of the structure of these compounds lies in the fact that they react quantitatively with mercuric chloride to give the original acetylated hydroxyphenylmercuric chlorides.

$$2CH_3CO\text{–}OC_6H_4\text{–}HgCl + 2Na_2S_2O_3 = (CH_3CO\text{–}OC_6H_4)_2Hg + Na_2Hg(S_2O_3)_2 + 2NaCl.$$

$$(CH_3CO\text{–}OC_6H_4)_2Hg + HgCl_2 = 2CH_3CO\text{–}OC_6H_4\text{–}HgCl.$$

Dimroth was able to change the *o*-hydroxyphenylmercuric chloride to the corresponding mercury diphenyl derivative but did not carry out the reaction with the *para* compound. Dimroth's work was repeated and confirmed. It seemed possible that the missing *para* mercury diphenyl derivative might be made by saponifying the corresponding acetylated substance. When this was tried the product was found to be a monophenylmercuric derivative. In other words, one of the phenyl groups had been removed from the mercury by the action of hot sodium hydroxide. Apparently this is a new method of splitting a Hg-C linkage. It is another example of the "loosening" effect of hydroxyl or, in this case of the ONa group, on a mercury atom attached to the same nucleus. The reactions involved may be written thus:

$$(CH_3CO\text{–}OC_6H_4\text{–})_3Hg + 4NaOH = (NaO\text{–}C_6H_4\text{–})_2Hg + 2CH_3CO_2Na + 2H_2O$$

$$2(NaO\text{–}C_6H_4\text{–})_2Hg + H_2O = NaO\text{–}C_6H_4\text{–}HgOH + C_6H_5ONa$$

Neutralization with dil. acetic acid precipitated $(HO\text{–}C_6H_4\text{–}Hg)_2O$ instead of the corresponding hydroxide.[1] An analogous reaction occurs and a similar product is obtained with the acetylated *ortho* diphenyl derivative. Both the complex organomercuric oxides were converted to the original chlorides by treatment with acetic acid and sodium chloride. The same conversion was brought about by treatment with ethyl acetate and then with sodium chloride solution.[2] All the organic mercury compounds studied reacted with ammonium sulfide only on standing. They reacted slowly with cold conc. hydrochloric acid, but rapidly with the hot acid to give inorganic mercury salts which formed an immediate precipitate with hydrogen sulfide.

Experimental.

Preparation of the *o*- and *p*-Hydroxyphenylmercuric Chlorides.—Twelve g. of phenol (about 1.5 molecules) was heated on the steam-bath and 25 g. of mercuric acetate was added gradually while the mixture was stirred constantly. When all the acetate had dissolved, boiling water was added and the mixture was boiled for a few minutes. Then a hot solution of 5 g. of sodium chloride was added. The *p*-hydroxyphenylmercuric chloride precipitated at once. The mixture was filtered while hot. The solution, on standing, deposited crystals of the *ortho* compound. The properties of these substances agreed with those recorded by Dimroth. When the preparation was carried out as described, no dimercury compound was formed. This was proved by the complete solubility of the mixture in boiling water. The amounts of *ortho* and *para* compounds formed varied only slightly with the temperature of reaction. With 25-g. portions of mercuric acetate (about 85% pure), the following amounts of *para* and *ortho* compounds were obtained, at 100°, 18 g. of *para* and 7 g. of *ortho*; at 125°, 16 g. of *para* and 8 g. of *ortho*; at 150°, 14 g. of *para* and 8 g. of *ortho*.

Preparation and Properties of the Acetyl Derivatives of the Hydroxyphenylmercuric Chlorides.—Fourteen g. of the *o*-hydroxyphenylmercuric chloride was treated with a slight excess of acetyl chloride (3 cc.) and warmed gently. After the evolution

[1] Compare Dimroth, *Ber.*, **35**, 2854 (1902).

[2] Compare THIS JOURNAL, **41**, 1854, Summary, 3 (1921).

of hydrochloric acid had ceased, the substance was pressed on a porous plate and then washed many times with water. Twelve g. of the acetyl derivative was obtained (about an 80% yield). The *para* compound was prepared in a similar way. Melting points (uncorr.): *ortho*, 170–1°; *para*, 235°.

Analyses.—Calc. for C_8H_7OClHg: Hg, 54.05. Found: *ortho*, 54.1, 54.0, 54.0; *para*, 53.8, 53.5.

Reaction of Potassium Iodide with the Mercurated Phenols.—When the *o*-hydroxyphenyl mercuric chloride, the corresponding *para* compound, and the *o,p*-diacetoxymercuriphenol were boiled with excess of potassium iodide solution they dissolved, the solutions became alkaline, and phenol and inorganic mercury compounds were formed. The alkali was titrated with standard acid. The procedure was as follows. 1 g. of the mercury compound was boiled for half an hour with 50 cc. of water and 2 g. of potassium iodide. Water was added to replace that lost by evaporation. The base was then titrated with 0.1 *N* sulfuric acid. One g. of the *o*-hydroxyphenylmercuric chloride gave 30.12 cc. of 0.1 *N* potassium hydroxide, while that calculated was 31.90. One g. of the *para* compound gave 29.12 cc. of 0.1 *N* potassium hydroxide, as compared with calculated 31.90 cc. One g. of the dimercury acetate compound gave 32.50 cc. of 0.1 *N* hydroxide, compared with 32.6 cc. calculated for 2 molecules.

An experiment was tried with the *ortho* compound in which potassium bromide or chloride was used instead of the iodide. The compound boiled with the chloride gave no alkali. Long boiling of it with the bromide gave only a slight alkalinity. Similar results were obtained with the *para* and with the di-compounds.

Reaction of Potassium Iodide with the Acetylated Compounds.—When the acetyl derivative of the *o*- or *p*-hydroxyphenylmercuric chlorides was boiled with potassium iodide solution, no alkali or phenol was formed. Thus, 1.5 g. of the *ortho* acetylated compound was boiled for one hour with 50 cc. of water and 2 g. of potassium iodide. The solution was still neutral. The solution was distilled with steam and the distillate was tested with ferric chloride. No color resulted. When the aqueous filtrate from the organomercuric iodide was cooled, it yielded 0.2 g. of white needle shaped crystals melting at 125°. This substance was proved to be the mercury diphenyl derivative, mercury di-(*o* hydroxyphenyl acetate), $(CH_3CO\text{-}OC_6H_4\text{-})_2Hg$. The yield was only about 20%. The *para*-acetylated compound is changed to the organomercuric iodide only after long boiling with potassium iodide.

Reaction of Sodium Thiosulfate with the Acetylated Compounds.—Seven g. of the *ortho* acetyl derivative was dissolved in a thiosulfate solution containing 15 g. of the crystalline salt in 100 cc. of water. The mercury compound dissolved fairly readily to give a clear solution. As this solution stood, crystals of the mercury diphenyl compound separated. After 3 days, 3.6 g. of the *o, o'*-mercuribisphenol diacetate had separated as white needles, m. p. 125°. Yield, about 80%. They are slightly soluble, on heating, in alcohol, in benzene, and in chloroform; very slightly soluble in ether.

Analyses.—Calc. for $C_{16}H_{14}O_4Hg$: Hg, 42.62. Found: 42.7, 42.0.

Similarly, the *para* acetylated compound was treated with thiosulfate. The *para* diphenyl derivative separated from the thiosulfate solution as white crystals, m. p. 172–3°, much more slowly than did the *ortho* compound. The yield was poorer; 10 g. of the chloride gave only 3 g. of the diphenyl compound, about a 50% yield.

Analyses.—Calc. for $C_{16}H_{14}O_4Hg$: Hg, 42.62. Found: 42.4, 42.3.

Reaction of Mercuric Chloride with the Acetylated Diphenyl Derivatives.—The structure of the diphenyl derivatives was proved by splitting them with mercuric chloride to form the original chlorides. One g. of the *ortho* diphenyl derivative was boiled with 50 cc. of water containing 0.5 g. of mercuric chloride and yielded 1.4 g. of the *ortho* $CH_3CO\text{-}OC_6H_4\text{-}HgCl$, m. p. 170°. Similarly, the *para* diphenyl compound gave the original chloride (m. p. 235°), quantitatively.

Reaction of the Acetylated Mercury Compounds with Sodium Hydroxide.—Three g. of the *ortho* acetylated mercury diphenyl compound was boiled for 20 minutes with 50 cc. of 5% sodium hydroxide. The solution was cooled and made exactly neutral with dil. acetic acid. One and seven-tenths g. of a white amorphous substance separated. It did not melt, but darkened at a high temperature. Analyses indicated that it was the oxide obtained by Dimroth, di(hydroxyphenylmercuric) oxide.

Analyses.—Calc. for $C_{12}H_{10}O_3Hg_2$: Hg, 66.5. Found: Hg, 67.0, 66.7, 66.2.

When treated with dil. acetic acid and sodium chloride it gave the original chloride, hydroxyphenylmercuric chloride. When the oxide was boiled with ethyl acetate it dissolved readily. When this solution was boiled with sodium chloride solution the original chloride was formed.

The acetylated *para* mercury diphenyl compound was split in the same way by boiling with dilute sodium hydroxide. A similar complex oxide was formed. Like its isomer it was amorphous and did not melt.

Analyses.—Calc. for $C_{12}H_{10}O_3Hg_2$: Hg, 66.5. Found: Hg, 66.8, 67.0.

This complex oxide was changed to the *p*-hydroxyphenylmercuric chloride by treatment with dilute acetic acid and sodium chloride, and, also, by treatment with ethyl acetate and sodium chloride.

Reaction of the Acetylated Compounds with Sulfides and with Acids.—The *ortho* and *para* acetylated hydroxyphenylmercuric chlorides suspended in water and treated with hydrogen sulfide for 15 minutes gave no mercuric sulfide. After contact with ammonium sulfide for about half an hour, they commenced to blacken. The free mercury phenols acted a little more rapidly. The acetylated mercury diphenyl compounds gave no action with ammonium sulfide in less than 3 days; then a red precipitate began to form.

The acetylated hydroxyphenylmercuric chlorides treated with conc. hydrochloric acid and hydrogen sulfide showed no reaction. After standing for half an hour, or if they were heated, mercuric sulfide was formed. The acetylated mercury diphenyl compounds treated with conc. hydrochloric acid and hydrogen sulfide gave no mercuric sulfide, until the mixture had stood for about an hour or had been heated.

Summary.

1. Mercuric acetate reacts with an excess of phenol in the absence of a solvent to form only the *ortho* and *para* mercurated phenols. This differs from the action in water which gives a large amount of the diproduct even in the presence of a large excess of phenol.

2. The hydroxyphenylmercuric chlorides and the corresponding dimercury acetate are split by iodides; mercuric iodide, phenol, and a base are formed. Bromides cause a partial splitting, chlorides none at all.

3. The acetylated compounds are not split by potassium iodide in the way that the phenols are. They give the organomercuric iodides and, in the case of the *ortho* compound, a small amount of the corresponding mercury diphenyl derivative.

4. Both of the acetylated chlorides react with conc. sodium thiosulfate solution to give the corresponding acetylated mercury diphenols.

5. The acetylated mercury diphenols, when treated with dil. sodium hydroxide, not only lose the acetyl groups but suffer a splitting of the Hg-C linkage which leaves a monophenylmercuric derivative. This, apparently, is a new method of breaking an Hg-C bond.

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SOME MERCURY DERIVATIVES OF PHENOL ETHERS[1]

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In an earlier paper[3] it was shown that mercurated phenols react with iodides of alkali metals to give the original phenols, inorganic mercury compounds and 1 equivalent of alkali for each carbon-mercury linkage broken. When, however, the hydroxyl group is protected by acylation iodides react in quite a different way giving mercuri-bis compounds and inorganic mercury compounds but not alkali. The two processes may be illustrated as follows.

$$HO—C_6H_4—HgI + 3\,KI + H_2O \longrightarrow C_6H_6OH + K_2HgI_4 + KOH$$
$$2\,AcO—C_6H_4—HgI + 2\,KI \longrightarrow (AcO—C_6H_4)_2Hg + K_2HgI_4$$

The present work was undertaken to determine the effect of replacing the phenolic hydrogen by an alkyl group instead of an acyl group. An observation made by Dimroth[4] indicated that the effect of the 2 groups might be similar. In determining the structure of *o*-chloromercuri-phenol, he treated it with ethyl iodide in alkaline alcoholic solution to prepare the known *o*-phenetylmercuric iodide. Besides the desired product he obtained a good yield of *o*-mercury-diphenetyl. Since sodium iodide is formed in the reaction it seemed reasonable that it might change the mercurated phenetole first formed to the mercuri-bis compound. Dimroth's results may then be formulated as follows.

$$NaO—C_6H_4—HgCl + RI \longrightarrow RO—C_6H_4—HgCl + NaI$$
$$2\,RO—C_6H_4—HgCl + 4\,NaI \longrightarrow (RO—C_6H_4)_2Hg + Na_2HgI_4 + 2\,NaCl$$

In order to test this theory and to study further the effect of protecting a phenolic hydroxyl group upon the stability of the carbon-mercury linkage, the action of potassium iodide on mercurated phenol ethers was studied.

Iodomercuri-anisoles and -phenetoles were prepared by the method of Dimroth.[4] As the *ortho* mercurated compounds are much more soluble than the *para* compounds, the study was limited to the former. When an alcoholic solution of *o*-iodomercuri-anisole or of *o*-iodomercuri-phenetole is refluxed with potassium iodide, no splitting of the carbon-mercury linkage takes place as no alkali is formed. *o*-Mercury-dianisyl or *o*-mercury-diphenetyl is obtained in good yield. The mother liquors contain large amounts of inorganic mercury compounds. Potassium thiocyanate acts

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[2] Research Fellow under a grant from the U. S. Interdepartmental Social Hygiene Board, General M. W. Ireland, Chairman. Some of the organic mercury compounds related to those studied are being investigated pharmacologically under the direction of Dr. A. S. Loevenhart of the Department of Pharmacology of the University of Wisconsin.

[3] This Journal, **43**, 622 (1921).

[4] Dimroth, *Ber.*, **32**, 763 (1899).

like potassium iodide but gives poorer yields of the mercuri-bis compounds.

The *para* mercurated phenol ethers react to some extent with potassium iodide or with potassium thiocyanate; some inorganic mercury is formed. No alkali is found. The corresponding mercuri-bis compounds are not obtainable in a pure state by these reactions.

Sodium thiosulfate is the most convenient reagent for making the mercuri-bis compounds of the phenol ethers. The *o*-iodomercuri compounds dissolve readily in it giving solutions from which the mercuri-bis compounds separate on standing.

o-Mercury-dianisyl and *o*-mercury-diphenetyl react normally with mercuric chloride; quantitative yields of the chloromercuri compounds are obtained.

Experimental Part

Preparation of *o*- and *p*-Iodomercuri-phenetoles.—A mixture of 5 g. of *o*-chloromercuri-phenol[3] in 50 cc. of 50% ethyl alcohol, 0.7 g. of sodium hydroxide, and 3.5 g. of ethyl iodide is heated gently for 1 hour. A small amount of *o*-mercury-diphenetyl separates as the solution cools. This is removed and the filtrate is diluted with water to precipitate the *o*-iodomercuri-phenetole which is recrystallized from alcohol; yield, 7 g. The *para* compound is prepared in a similar way. Five g. of *p*-chloromercuri-phenol gives 5 g. of a mixture of the corresponding iodomercuri and mercuri-bis-compounds which is difficult to separate. Because the *ortho* compounds are obtained more easily, the experiments with potassium iodide, with thiocyanate, and with thiosulfate were carried out with *o*-iodomercuri-phenetole and *o*-iodomercuri-anisole.

Preparation of *o*-Iodomercuri-anisole.—Eight g. of *o*-chloromercuri-phenol, 1 g. of sodium hydroxide, 50 cc. of alcohol, and 3 g. of methyl iodide are heated for half an hour. About 1 g. of *o*-mercury-dianisyl separates as the solution cools. Dilution of the mother liquor with water gives 7 g. of the iodomercuri compound.

Reaction of Potassium Iodide with *o*-Iodomercuri-anisole and with *o*-Iodomercuri-phenetole.—Four g. of *o*-iodomercuri-anisole, recrystallized from alcohol, is heated under a reflux condenser for 6 hours with 3 g. of potassium iodide and 50 cc. of alcohol. When the product is cooled and diluted somewhat the *o*-mercury-dianisyl is precipitated. It is recrystallized from alcohol; yield, 1.5 g.; m. p., 108°. The filtrate from the reaction mixture is neutral and gives an immediate precipitate with hydrogen sulfide.

A solution of 2 g. of *o*-iodomercuri-phenetole in 50 cc. of alcohol together with 2 g. of potassium iodide is refluxed for 1 hour. When this product is cooled and diluted with water, 1.5 g. of *o*-mercury-diphenetyl separates. After crystallization from alcohol it melts at 81°. The filtrate is not alkaline. It contains inorganic mercury compounds.

Reaction of Potassium Thiocyanate with the *o*-Iodomercuri-phenol Ethers.—A mixture of 2 g. of *o*-iodomercuri-anisole, 2 g. of potassium thiocyanate and 50 cc. of alcohol was heated under a reflux condenser for 3 hours. The product, cooled and diluted, gave 1.5 g. of the mercuri-bis compound. Recrystallization from alcohol raised the melting point only to 75–80°. The filtrate contains inorganic mercury compounds but is neutral.

A mixture of 1.6 g. of *o*-iodomercuri-phenetole, 2 g. of potassium iodide and 50 cc. of alcohol, heated under a reflux condenser for 3 hours gives 0.8 g. of the mercuri-bis compound melting at 80° after several crystallizations from alcohol.

Reaction of Sodium Thiosulfate with the *o*-Iodomercuri-phenol ethers.—Two g. of *o*-iodomercuri-phenetole dissolved in a solution of 4 g. of sodium thiosulfate in 50 cc. of water deposits 1.2 g. of the mercuri-bis compound on standing; m. p., 81–83°.

Similarly, *o*-iodomercuri-anisole gives the mercuri-bis compound melting at 108°.

Reaction of the *p*-Iodomercuri-phenol Ethers with Potassium Iodide and with Potassium Thiocyanate.—The reactions between these substances apparently lead to the formation of mercuri-bis compounds, as the filtrates contain inorganic mercury and are not alkaline. However, the products are very difficult to purify.

Reaction of Mercuric Chloride with the Mercuri-bis-phenol Ethers.—One g. of *o*-mercury-dianisyl is heated with 0.7 g. of mercuric chloride in 25 cc. of alcohol for 15 minutes. The chloride deposits on cooling, and is recrystallized from alcohol; m. p., 177–178°. Dimroth obtained the same compound in small amount by direct mercuration of anisole. He gives the melting point as 173–174°.

Similarly, *o*-mercury-diphenetyl reacts with mercuric chloride to give pure *o*-chloromercuri-phenetole.

Summary

1. Protection of the hydroxyl groups in mercurated phenols by alkylation has the same effect as protection by acylation, that is, the stability of the carbon-mercury linkage to iodides, thiocyanates, and to thiosulfates is increased.

2. Mercurated phenol ethers react with iodides, with thiocyanates, and with thiosulfates to form the corresponding mercuri-bis compounds giving solutions which contain inorganic mercury but no alkali, showing that the protection of the phenolic hydroxyl has prevented the splitting of the carbon-mercury linkage with the accompanying formation of alkali which occurs with the mercurated phenols.

3. The formation of the mercuri-bis compounds takes place much more readily in the case of the *ortho* compounds than with the *para* compounds.

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A similar product is formed from aniline and 5-acetoxymercuri-3-nitro-salicylaldehyde.

3-Chloromercuri-5-nitrosalicylal-aniline.—Three g. of the aldehyde dissolved in 8 cc. of hot aniline and cooled gives an orange-red product which is insoluble and does not melt.

Analyses. Calc. for $C_{13}H_9O_3N_2ClHg$: Hg, 42.1. Found: 42.5, 42.8.

Summary

1. Mercuration of salicylaldehyde by mercuric acetate gives mainly a dimercurated product with only small amounts of a monomercurated aldehyde.

2. The two nitro-salicylaldehydes give normal mercuration products.

3. The mercurated salicylaldehydes lose all their mercury when treated with potassium iodide, hydroxylamine or phenylhydrazine.

4. The mercurated salicylaldehydes form Schiff's bases with aromatic amines.

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